Paper No. 21

# UNITED STATES PATENT AND TRADEMARK OFFICE

## BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MARTIN C. WOODLE,
IRMA A.J.M. BAKKER-WOUDENBERG, and
FRANCIS J. MARTIN



Appeal No. 2001-2130
Application No. 09/139,058

ON BRIEF

Before WINTERS, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

VACATUR AND REMAND

The examiner has finally rejected claims 8, 9, and 11-19, all of the claims remaining. Claims 8 and 12 are representative and read as follows:

8. For use in a method of treating a site of systemic infection which is localized at a tissue site other than the fixed macrophages residing in the liver or the spleen, an injectable liposome composition which:

(a) is comprised of a vesicle-forming lipid and between about 1-20 mole percent of an amphipathic vesicle-forming lipid derivatized with a hydrophilic biocompatible polymer selected from the group consisting of polyglycolic acid (PGA), polylactic acid (PLA), a copolymer of PGA and PLA, polyvinyl alcohol and polyethyleneglycol, said polymer being of a size and in a molar amount effective to extend liposome

blood circulation time, measured 24 hours after said injection, over that achievable in the absence of the hydrophilic polymer,

(b) is composed of liposomes having a selected mean particle diameter in the size range between about 0.07-0.20 microns;

(c) contains in liposome-entrapped form, a therapeutic compound active against the pathogen causing the infection, and

(d) is able to accumulate selectively in the infected tissue following intravenous administration, thereby to concentrate liposome-entrapped drug at the infection site.

12. The composition of claim 8, wherein the site of infection is the lung, and the aminoglycoside antibiotic is gentamicin.

The examiner relies on the following references:

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|---|---|---|
| Janoff et al. (Janoff) | 4,897,384 | Jan. 30, 1990 |
| Popescu et al. (Popescu) | 4,981,692 | Jan. 01, 1991 |
| Yoshioka et al. (Yoshioka) | 5,593,622 | Jan. 14, 1997 |

Claims 8, 9, and 11-19 stand rejected under 35 U.S.C. § 103(a) as obvious in view of either Janoff or Popescu, combined with Yoshioka.

For the reasons discussed below, we vacate the examiner's rejection and remand the application to the examiner for further consideration.

Technical Background

"Liposomes have been proposed as a drug carrier for intravenously (IV) administered compounds. . . . However, the use of liposomes for site-specific targeting via the bloodstream has been severely restricted by the rapid clearance of liposomes by cells of the reticuloendothelial system (RES)." Specification,

page 5. "Liposomal treatment of infections has therefore been largely limited to treatment of the reticuloendothelial system." Id. "[N]o single factor identified to date has been effective to provide long blood halflife, and more particularly, a relatively high percentage of liposomes in the bloodstream 24 hours after injection." Id.

The specification discloses that liposomes formed from an unmodified vesicle-forming lipid in combination with "an amphipathic vesicle-forming lipid having a derivatized hydrophilic polymer" have significantly enhanced blood circulation time, compared to liposomes formed from unmodified lipids alone. See pages 14-15. Compositions comprising such liposomes are disclosed to be useful in treating infections at sites outside the reticuloendothelial system, because they are taken up by cells of the RES less quickly than unmodified liposomes. See pages 6 and 29.

Procedural Background

According to Appellants, the present application is a divisional of application 07/858,171, which issued as U.S. Patent 5,843,473. The '171 application was a continuation-in-part of application 07/642,231, which in turn was a CIP of application 07/425,224. The '231 and '224 applications issued as U.S. Patents 5,213,804 and 5,013,556, respectively.

## Discussion

Claim 8 is representative of the claimed invention. Claim 8 is directed to a composition comprising liposomes made of a "vesicle-forming lipid" and an "amphipathic vesicle-forming lipid derivatized with a hydrophilic biocompatible polymer." The polymer can be, e.g., polyethylene glycol, and the derivatized lipid is present in an amount of 1-20 mole percent. The liposomes have a "mean particle diameter" of 7-20 microns and contain a therapeutic compound entrapped within them.

The examiner rejected the claims as obvious over either of Janoff or Popescu, combined with Yoshioka. The examiner relied on Janoff and Popescu, alternatively, for their disclosure of gentamicin-containing liposomes. See the Examiner's Answer, page 3. The examiner acknowledged, however, that neither Janoff nor Popescu taught derivatizing the liposome-forming phospholipids with a hydrophilic polymer such as polyethylene glycol (PEG). The examiner cited Yoshioka as teaching this limitation:

> Yoshioka teaches that when phospholipids which are attached to PEG are used in the formation of liposomes, the hydrophilic moiety of PEG prevents the adsorption of plasma proteins on the liposomes and the subsequent agglutination of liposomes (note the abstract).

Examiner's Answer, pages 3-4. The examiner concluded that "[t]he attachment of PEG to the surface of the liposomes (by coupling with the phospholipid) taught by Janoff or Popescu would have been obvious to one of ordinary skill in the art because PEG prevents the adsorption of plasma proteins on the liposomes and the subsequent agglutination of liposomes as taught by Yoshioka." Id., page 4.

Appellants argue that those skilled in the art would have recognized that the liposomes disclosed by Janoff and Popescu would not have functioned for their intended purpose if modified in the manner taught by Yoshioka. Therefore, Appellants argue, a person of ordinary skill in the art would not have been motivated to combine the references. See, e.g., Appeal Brief, page 5.

Appellants' arguments raise issues that cannot satisfactorily be resolved on this record. With respect to the rejection over Janoff and Yoshioka, Appellants argue that the PEG-derivatization of the polar head group of the phospholipids in Janoff's liposomes would prevent them from interacting with the entrapped drug or its toxicity receptor, and therefore defeat the stated purpose of Janoff's invention. Appeal Brief, pages 6-7. As evidence supporting their position, Appellants cite two references that purportedly were "previously submitted." See notes 1 and 2 on page 7. Appellants, however, do not specify when the references were submitted, or where in the record they can be found. We have reviewed the record and have not found either of the cited references or any evidence that they were submitted during prosecution.

For his part, the examiner did not substantively respond to Appellants' reliance on these references. Instead, the examiner presented an argument based on Janoff's disclosure that PEG-cholesterol effectively inhibits the growth of C. albicans. Examiner's Answer, page 4. As Appellants point out, however, Janoff discloses that PEG-cholesterol does not form liposomes (column 11, line 60 to column 12, line 6), and therefore the examiner's reliance on this example seems misplaced.

Thus, Appellants' assertion that PEG-derivatization would defeat the purpose of Janoff's invention has not been supported by evidence, but neither has it been rebutted by the examiner. The record has not been sufficiently developed to allow us to decide the merits of this rejection. Upon return of this case, the examiner should clarify whether the references cited by Appellants have in fact been submitted, and if they have, the examiner should respond substantively to Appellants' argument based on them.

The rejection based on Popescu presents even more vexing questions. On this rejection, Appellants argue that Popescu's invention is based on drug-laden liposomes being taken up by macrophages of the RES system. Appeal Brief, page 8. Appellants also argue that a person of ordinary skill in the art would not have been motivated to combine Popescu and Yoshioka, because PEG-derivatized liposomes were well-known not to be taken up by the RES system. As support for this latter assertion, Appellants cite the '556 patent that issued from application 07/425,224, to which the instant application claims benefit under 35 U.S.C. § 120. See the Appeal Brief, page 5. It is Appellants' reliance on the '556 patent that puts us in a predicament.

In order for Appellants' argument to have merit, and to overcome the rejection, the '556 patent must be available as prior art. If it is not prior art, its disclosure does not provide evidence of what was known as of the effective filing date of the present claims, and therefore cannot be relied on as evidence that the claimed invention would have been nonobvious, at that time. See In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)

("Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.").

Of course, if the '556 patent is prior art, then it is prior art for all purposes, including anticipation under 35 U.S.C. § 102(e) and obviousness under 35 U.S.C. § 103. In fact, if it is prior art, the '556 patent would appear to be the closest prior art in the record. The '556 patent discloses

> a liposome composition for administering a drug via the bloodstream. The composition includes liposomes containing the drug in liposome-entrapped form, and between 1-20 mole percent of an amphipathic lipid derivatized with a polyalkylether. One preferred amphipathic lipid is a phospholipid, such as phosphatidylethanolamine, derivatized with polyethyleneglycol. The liposomes in the composition preferably have a selected average size in the size range between about 0.05 and 0.5 microns.

Column 4, lines 44-53. The '556 patent also discloses that such liposomes have prolonged blood circulation times (column 11, lines 35-50) and are able to target specific tissues or organs outside the RES (column 12, lines 42-47).

The examiner has not determined on the record the effective filing date of the claims, i.e., whether the claims are entitled to § 120 benefit based on the application that matured into the '556 patent. In order for the instant claims to be entitled to the benefit of the '556 patent's filing date, the '556 patent must provide an adequate written description and an enabling disclosure of the invention now

claimed. See, e.g., In re Chu, 66 F.3d 292, 297, 36 USPQ2d 1089, 1093 (Fed. Cir. 1995) ("It is elementary patent law that a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112."). See also Chester v. Miller, 906 F.2d 1574, 1577, 15 USPQ2d 1333, 1336 (Fed. Cir. 1990): "[A]lthough a patent might contain a disclosure satisfying the written description requirement with respect to the claims in that patent, it could still be section 102(b) prior art as to broader claims of a subsequent application although not containing a disclosure satisfying the section 112 description requirement with respect to the anticipated broader claims. . . . This apparent anomaly is most likely to occur when the prior art reference discloses a species of a genus sought to be claimed."

Based on a cursory review of the '556 patent, its disclosure of hydrophilic polymers appears to be limited to "polyethyleneglycol and related homopolymers." See column 6, lines 10-17. The patent does not appear to disclose the other hydrophilic polymers recited in the instant claims (polyglycolic acid, polylactic acid, a copolymer of PGA and PLA, or polyvinyl alcohol). Thus, the '556 patent does not appear to provide a description of liposomes derivatized with a polymer other than PEG, as presently claimed in, e.g., claim 8. Thus, it would seem that the instant claims are not adequately described by the '556 patent and are therefore not entitled to the benefit of priority. If this is the case, the '556 patent is available prior art, and is closer prior art than any of the references cited by the examiner.

We emphasize that we are not finding, as a matter of fact, that the '556 patent does not adequately describe the instant claims, nor are we concluding that the claims are not entitled to priority under § 120. The examiner is in a better position to make those determinations.

On return of this case, the examiner should determine, on the record, whether or not the instant claims are entitled to the effective filing date of the '556 patent under 35 U.S.C. § 120. If the claims are not entitled to § 120 benefit based on the '556 patent, the examiner should determine whether the '556 patent is available as prior art (e.g., under 35 U.S.C. § 102(e)) and determine whether it renders the instant claims unpatentable for anticipation or obviousness.

Summary

The record does not allow us to decide the merits of the rejections on appeal. The rejection over Janoff is problematic because the references cited by Appellants do not appear to be in the record, yet the examiner has neither confirmed nor disputed what those references teach. Our review of the rejection over Popescu depends on whether the '556 patent qualifies as prior art, which in turn depends on the effective filing date of the instant claims. We therefore vacate the examiner's rejection and remand for action consistent with this opinion.

VACATED and REMANDED

Sherman D. Winters )
Administrative Patent Judge )
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)
Eric Grimes ) BOARD OF PATENT
Administrative Patent Judge ) APPEALS AND
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